

# Fabrication and Characterization of Electrospun Drug-eluting Nanofibers from Polycaprolactone/Chitosan Blends

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## Abstract

Electrospinning has emerged as a widely accepted technique with ability to produce nanofibers that can be employed in many biomedical applications. In particular, drug-eluting nanofibers have become very popular in controlled release of small molecule drugs. In this study, nanofibers from blends of polylactocaprone (PCL) and chitosan (CHI) were electrospun with the ability to load a model drug, acetylsalicylic acid (ASA), at 10 wt%. PCL/CHI fibers exhibited smooth surface morphology at polymer compositions ranging from 100/0 to 40/60 with or without the incorporation of ASA. Mechanical properties suggested a brittle failure mechanism for fibers loaded with drug. In vitro drug release study displayed a controlled release profile of ASA up to 48 h. Our study aims to explore the drug-polymer interactions and their effects on fiber structure, mechanical properties and drug release profile.

## 1. Introduction

In the field of drug release, there are many different routes to administer drugs for cells/tissues uptake. Among them, electrospun nanofibers have shown several advantages for topical administration on mucosal sites. These advantages include the ability to achieve high drug loading (up to 60%) and encapsulation efficiency (up to 100%), to incorporate various polymers for accommodations of a wide variety of biological agents, to modulate release, and to provide process simplicity and cost-effectiveness [1].

Electrospinning is a process that continuously draws nanofibers through an electric field. A typical setup of electrospinning consists of a syringe with a needle tip attached to it, a syringe pump, a stationary plate collector, and a voltage source (Figure 1). During the electrospinning process, polymer solution is pumped through the needle tip of the syringe at a constant flow rate. The voltage source creates a surface charge density that, for successful electrospinning to occur, must overcome the surface tension of the polymer solution to produce fibers. The negative portion of the voltage source is

connected to the plate collector at a certain distance from the needle tip, resulting an electric field between the needle tip and collector. This electric field forces fibers to travel and deposit on the plate collector through rapid solvent evaporation, and thus creating a fiber mat [2].

Nanofibers created through electrospinning have been used for many applications such as defense, environmental engineering, and healthcare [3]. Electrospun nanofibers have also been used in the field of controlled drug release. With the numbers of biocompatible polymers that are available for electrospinning, fibers produced from electrospinning have become very popular in the field of drug release. In this study, polymer solutions of polycaprolactone (PCL) and chitosan (CHI) at various blend ratios were electrospun into fibers. Both PCL and CHI are biodegradable and biocompatible [4], whereas PCL is a hydrophobic synthetic polymer and CHI is a hydrophilic natural polymer. We hypothesize that drug release from PCL/CHI fibers is modulated through hydrophilic/hydrophobic components from polymer matrix. In addition, drug-polymer interactions attribute to effects in mechanical properties and drug release profiles [5]. As a result, we aim to study both effects to provide scientific understanding on small molecule drug release from electrospun nanofibers and to further inform the development of drug-eluting nanofibers for controlled release purpose.

## 2. Materials and Methods

### 2.1 Materials

Chitosan powder (90% deacetylation) was obtained from Xi'an Zhongyun Biotechnology Co., Ltd. (China). Polycaprolactone ( $M_w = 80\text{KDa}$ ) was obtained from Huaian Ruanke Co., Ltd. (China). Glacial acetic acid (AA), hexafluoro-2-propanol (HFIP), and phosphate-buffered saline (PBS) were obtained from VWR Analytical. Acetylsalicylic acid (ASA) (99% purity) was obtained from Alfa Aesar. All the other chemicals were of reagent grade and used as received without further purification.

### 2.2 Preparation of Electrospun PCL/CHI fibers

15 wt% of PCL was dissolved in HFIP and 4 wt% of CHI was dissolved in 90% AA/DI water (v/v) mixture. The solutions were combined to create blend solutions at ratios 100/0, 80/20, 60/40, and 40/60 PCL/CHI. ASA was added to blend solutions at 10 wt% (w/w = wt%). All solutions were allowed to mix overnight before electrospinning. Electrospinning was carried out using a 2 mL syringe with a 25 G blunt-end needle, 20  $\mu\text{L}/\text{min}$  flow rate, 14-17 kV of voltages, and a distance of 7 to 9 cm from the tip of the needle to the stationary collector plate.

### 2.3 SEM Imaging and Material Characteristics

Fiber morphologies and fiber diameters were analyzed by using a JOEL scanning electron microscopy. Circular punches were taken from the fiber mats and sputter coated with Au/Pd for 30 s using a sputter-coater. SEM micrographs were acquired at 5 kV, using a spot size 3, and a working distance of 15.0 cm. Fiber diameters were measured using an image analysis tool (ImageJ) ( $n = 70$ ).

Fiber uniformity measurements were performed by a thickness gage (resolution = 0.01 mm). A 15 x 15 cm square paper with 10 mm grids was used to determine the location for thickness collection.

### 2.4 Mechanical Testing

Mechanical testing was performed on an Instron 3342 equipped with a 100 N load cell. Dog-bone samples (ASTM standard D1708-96) were created using a stainless steel die (ODC Tooling and Molds, Waterloo ON, Canada). Samples were then mechanically stretched under 21°C and 55% RH ( $n = 3$ ). Tensile tests were performed at a strain rate of 0.01  $\text{s}^{-1}$  where load and displacement data were obtained. Young's modulus (linear region before 2% strain) and tensile strength (zero slope) were calculated from each corresponding stress-strain curve.

### 2.5 In Vitro Drug Release Study

$\frac{1}{2}$ " diameter disks were cut from the fiber mats using a metal die. The mass for each sample was taken and theoretical drug loading was calculated. Disk samples were then placed in glass vials containing 10 mL of PBS as the release media and incubated at 37°C using an orbital shaker at 100 rpm (ThermoFisher). 200  $\mu\text{L}$  of the liquid samples were then taken at time intervals of 1, 4, 8, 24, and 48 h.

HPLC analysis was used to quantify ASA concentration in the release media. A Waters UV-HPLC system equipped with a C18 column was used to quantify drug levels in samples. The HPLC mobile phase consisted of a 50% HPLC graded  $\text{H}_2\text{O}$  and 50% acetonitrile. The HPLC methods included 25 °C column temperature, 1 mL/min flow rate, 5 min run time, 10  $\mu\text{L}$  sample injection volume and UV/vis detection at 270 nm and 295 nm for acetylsalicylic acid and salicylic acid, respectively. An ASA standard curve was developed by series dilution at concentrations of 200, 100, 50, 10, and 0.1  $\mu\text{g}/\text{mL}$ .

## 3. Results and Discussion

### 3.1 Fiber Structure and Uniformity

PCL/CHI nanofibers were produced at CHI concentration up to 60% in the fiber. Both blank and drug-loaded fibers (PCL/CHI = 60/40) exhibited a smooth and defect-free surface with no morphological changes (Figure 2). Average fiber diameters (PCL/CHI = 60/40) were  $293 \pm 44 \mu\text{m}$  and  $258 \pm 46 \mu\text{m}$  for blank and drug-loaded fibers, respectively. Average fiber diameter was slightly lower for the drug-loaded fibers perhaps due to the addition of the ASA increasing the spinnability of the fibers. Uniformity measurements on blank fiber mat (PCL/CHI = 100/0) revealed that fibers were mostly deposited at the center of the collection plate and gradually leveled off toward outer area (Figure 3).

### 3.2 Mechanical Testing

Representative engineering stress and engineering strain curves of blank and drug-loaded fibers (PCL/CHI = 100/0 and 40/60) showed an initial elastic region followed by failure at tensile strength (Figure 4A and 4B). Interestingly, blank fibers at all compositions exhibited significantly higher ductility than the drug-loaded fibers. In contrast, drug-loaded fibers displayed a dependence of stiffness and tensile strength on composition of chitosan in the fibers, suggesting a strong drug-polymer interaction. Our finding is in accordance with previous work [6].

Quantitative analysis on the mechanical properties showed that average Young's modulus and tensile strength of the drug-loaded fibers at PCL/CHI = 80/20 and 60/40 were significantly higher than those of the blank fibers ( $p > 0.05$ ) (Figure 5A and 5B). The average Young's moduli of drug loaded fibers were  $17.6 \pm 4.9$ ,  $43.1 \pm 2.4$ ,  $41.1 \pm 27.8$ , and  $38.6 \pm 18.4 \text{ MPa}$  for PCL/CHI blends of 100/0, 80/20, 60/40, and 40/60, respectively. These values were much higher than the Young's moduli of the blank fibers at  $12.4 \pm 1.4$ ,  $17.1 \pm 1.6$ ,  $13.3 \pm 9.3$ , and  $27.3 \pm 6.2 \text{ MPa}$  of the corresponding PCL/CHI compositions. Similarly, tensile strength of the drug-loaded fibers were  $1.2 \pm 0.5$ ,  $2.5 \pm 0.4$ ,  $2.1 \pm 0.2$ , and  $0.6 \pm 0.1 \text{ MPa}$  when increasing chitosan composition in the fibers, which were higher than the corresponding blank fibers of  $2.2 \pm 0.2$ ,  $1.8 \pm 0.7$ ,  $1.7 \pm 1.4$ , and  $0.9 \pm 0.5 \text{ MPa}$ . The differences in these values indicate that there is a strong drug-polymer interaction resulting in the change of mechanical properties.

### 3.2 Drug Release

As mentioned previously, electrospun nanofibers have the ability to provide a controlled release mechanism due to hydrophobicity/hydrophilicity of the polymer matrix and loading of the drug [7]. In particular, hydrophilic small molecule drugs loaded in PCL typically shows a burst release within 24 h [6]. As a result, we explore the release profiles of ASA from various compositions of PCL/CHI fibers (Figure 6). As shown in the graph, the release profile of ASA showed a sustained release behavior from pure PCL fibers over 2 days while increasing chitosan composition increased the release rate of ASA. Cumulative ASA released from PCL/CHI (100/0) fibers exhibited a steady increase from 4 h to 48 h, showing a zero-order release kinetic, suggesting that the current fiber

platform can be used for controlled release of hydrophilic small molecule drugs.

#### 4. Summary

This study aims to investigate the ability to electrospin PCL/CHI fibers and the ability to load a hydrophilic drug (ASA) at high loading (10 wt%). In addition, characterizations of the fibers showed a strong drug-polymer interaction in PCL/CHI fibers. We found correlations between fiber diameters and the presence of ASA with a significant change in mechanical properties. Our results showed that the incorporation of drug in the fibers modified the mechanical properties of these fibers. We were able to demonstrate the ability to sustain the release of ASA from the fibers. This study contributes to the scientific understanding of drug-polymer interactions on mechanical properties and controlled release of hydrophilic small molecule drugs.

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